Remarks

Reconsideration of this Application is respectfully requested.

Claims 166, 168, 170, 177 and 247 are pending in the application, with claim 166 being the independent claim.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

Interview of July 16, 2009

Applicants thank the Examiner for the discussion of the outstanding issues related to the above-captioned case at the Interview conducted on July 16, 2009 at the Examiner's office at the United States Patent and Trademark Office. Applicants appreciate the Examiner's taking time to provide feedback regarding the outstanding rejections.

Rejections under 35 U.S.C. § 103

Claims 166, 168, 170, 177 and 247 stand rejected under 35 U.S.C. § 103 as allegedly unpatentable over Chien *et al.* (U.S. Pat. No. 6,150,087), in view of Berzofsky *et al.* (U.S. Pat. No. 5,980,899) and Guo *et al.* (*Nature 360*:364-366 (1992)). (Office Action, page 3.) Applicants respectfully traverse the rejection.

The standard for obviousness is set forth in 35 U.S.C. §103 as follows:

> A patent may not be obtained though the invention is not identically disclosed as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to

> which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

35 U.S.C. §103(a) (2000).

The United States Supreme Court recently addressed the issue of obviousness in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 127 S.Ct. 1727 (2007). The Court stated that the *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966) factors provide a framework to make a determination of obviousness. Those factors are: 1) "the scope and content of the prior art"; 2) the "differences between the prior art and the claims"; 3) "the level of ordinary skill in the pertinent art"; and 4) objective evidence of nonobviousness. *KSR*, 127 S.Ct. at 1734 (*quoting Graham*, 383 U.S. at 17-18).

The Supreme Court in *KSR* also stated that "[w]hen there is a design need or market pressure to solve a problem and there are a *finite number* of identified, *predictable* solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. . . . [i]n that instance the fact that a combination was obvious to try might show that it was obvious under § 103." *See KSR* at 17 (emphasis added). This passage in KSR "posits a situation with a finite, and the context of the art, small or easily traversed, number of options that would convince an ordinarily skilled artisan of obviousness." *Ortho-McNeil Pharm., Inc. v. Mylan Labs, Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008).

As evidence of the scope and content of the prior art, the difference between the prior art and the claims, and unexpected results, Applicants provide the Declaration of one of ordinary skill in the relevant art, *i.e.* the researcher Dr. Alessandro Sette.

As discussed further below, Chien, Berzofsky and/or Guo do not offer a finite number of identified, predictable solutions to a person of ordinary skill in the art. Applicants therefore assert that the claimed invention is nonobvious over the prior art.

Chien discloses the sequence of the HCV genome, ~3000 amino acids in length. In columns 27-28, as noted in the Declaration of Dr. Alessandro Sette (Exhibit E), Chien lists a series of overlapping amino acid fragments arbitrarily generated and spanning the entire HCV genome. (Sette Declaration, ¶¶ 12-13.) The AA1850-AA1900 fragment, referenced by the Examiner in the Office Action, is only 1 of the 188 fragments listed in columns 27-28. (*Id.*, ¶ 12.) Each of these 188 fragments varies in size, from approximately 5 to 265 amino acids in length. Chien does not indicate whether any of the 188 individual fragments are preferable to any others.

Chien does not provide any guidance as to which particular fragment would be best suited to obtain an immunogenic HCV sequence. Looking at Chien, each of the 188 fragments would be an equally reasonable alternative with which to start in the process of selecting an antigenic peptide. In fact, Chien states that "[i]t is to be understood that these peptides do not necessarily precisely map one epitope, but may also contain HCV sequence that is not immunogenic." Chien, col. 27, lines 10-13. Furthermore, Chien, in discussing ways that one of ordinary skill in the art could apply techniques to identify potential immunogenic candidates, also notes that "[i]t is appreciated by those of skill in the art that such computer analysis of antigenicity does not always identify an epitope that actually exists, and can also incorrectly identify a region of the protein as containing an epitope." *Id.* at lines 4-8. Thus, as stated by Dr. Sette, Chien offers no further suggestion as to how to narrow down hundreds or even thousands of possible peptides

that could be generated by this brute force method to arrive at one, or even a reasonable number, of possible immunogenic peptides. (Sette Declaration, ¶ 15.) If one of ordinary skill in the art would look to Chien to identify an immunogenic peptide, he or she would find potentially hundreds or even thousands of different immunogenic epitopes that could be selected within all of the various fragments of the larger ~3000 amino acid sequence.

While the Examiner may now hone in on a particular fragment (AA1850-AA1900) using Applicants' claimed peptide as a starting point, this is applying hindsight reasoning in selecting which particular fragment, of the 188 disclosed in Chien, to use as a starting point. There is nothing in Chien that points to the AA1850-AA1900 fragment in particular, and without the knowledge of Applicants' claimed peptide being a CTL epitope, nothing in Chien would lead to Applicants' elected peptide, let alone the AA1850-AA1900 fragment that *comprises* the peptide.

In *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.* 492 F.3d 1350 (Fed. Cir. 2007), a post-*KSR* case, the Federal Circuit elaborated on the issue of obviousness where the prior art disclosed a large number of possible solutions. In its analysis, the Federal Circuit stated that

> Rather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation. . . . Thus, this case fails to present the type of situation contemplated by the Court when it stated that an invention may be deemed obvious if it was "obvious to try." The evidence showed that it was not obvious to try.

Takeda, 492 F.3d at 1359. The court in *Takeda* found that there was nothing in the prior art to suggest to one of ordinary skill in the art that any subset of disclosed compounds were better or superior to any of the others. *Id.*, 492 F.3d at 1359-1360.

The present case is similar to the situation in *Takeda*. In this instance, the cited references, at best, provide an extremely large number of epitopes upon which one of ordinary skill in the art can apply certain screening criteria, where the screening criteria provide no guarantee that an immunogenic CTL epitope will in fact be selected.

The Examiner notes that "Berzofsky et al. teach that it is desireable to identify CTL epitopes found in HCV." (Office Action, page 3.) However, "knowledge of the goal does not render its achievement obvious." *Abbott Labs v. Sandoz, Inc.*, 544 F.3d 1341, 1352 (Fed. Cir. 2008).

While Berzofsky generally describes other regions of HCV, it does not provide any guidance with regard to which specific regions of the HCV genome necessarily contain good targets for CTL, nor does it contain any guidance to identify Applicants' claimed peptide. A prior art reference must be considered in its entirety, including portions that would lead away from the claimed invention. *See* M.P.E.P. § 2141.02(VI) (citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983)); *see also Panduit Corp. v. Dennison Mfg. Co.*, 774 F.2d 1082, 1093-94 (Fed. Cir. 1985) ("The well established rule of law is that each prior art reference must be evaluated as an entirety . . . ."). That is, "[t]here is no suggestion to combine . . . if a reference teaches away from its combination with another source." *Tec Air, Inc. v. Denso Manufacturing Michigan Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999); *see also KSR* at 12 (reaffirming "the corollary principle that when the prior art teaches away from combining certain

known elements, discovery of a successful means of combining them is more likely to be nonobvious") (citing *United States v. Adams*, 383 U.S. 39, 51-52 (1966)).

Applicants' elected peptide, GVAGALVAFK, is neither discussed, nor described in Berzofsky. In addition, the peptides of Applicants' claimed invention are determined using techniques which do not rely on the amphipathicity algorithm of Berzofsky. Berzofsky does not disclose the techniques Applicants' utilized to identify candidate CTL epitopes. Therefore, at best, Berzofsky is an invitation to identify a peptide. Given the relatively large number of possible epitopes that could be identified within the HCV genome, the Berzofsky patent, without more, cannot be viewed to provide a sufficient reason to modify the art to arrive at Applicants' claimed invention. As such, Chien in view of Berzofsky does not render the claims obvious.

Furthermore, as noted by Dr. Sette, the presently claimed peptide is an NS4 (non-structural protein 4) peptide and Berzofsky provides no guidance to look for a peptide in the NS4 region. (*See* Sette Declaration, ¶ 20.) In fact, the primary focus of the Berzofsky study is to examine the role of 28 CTL epitopes derived from the HCV NS5 protein. (*See* col. 5, lines 23-38.) With respect to HCV NS4, Berzofsky discusses the lack of functional information regarding this region. In particular, Berzofsky states that "[t]he non-structural proteins are named NS1 through NS5, but the functions of only NS3 and NS5 have been assigned with certainty. NS3 is the viral protease and probably a helicase. NS5 is the viral RNA-dependent RNA polymerase." (Col. 1, lines 34-38.)

As noted by Dr. Sette, Berzofsky provides only very generic guidance to identify an HCV peptide epitope. Furthermore, Dr. Sette has opined that Berzofsky would not direct a researcher in the field to narrow down their potential search for epitopes to the

one particular region of HCV (NS4) in which the claimed peptide is located. (*See* Sette Declaration, ¶ 21.)

The Examiner has also alleged that:

> [O]ne of ordinary skill in the art would have been motivated to create the claimed peptide to screen for HCV peptides which were recognized by CTL because Berzofsky et al. teach that it is desirable to identify CTL epitopes found in HCV and Guo et al. teach that CTL recognize viral peptides complexed with MHC and that peptides which bind HLA-A268 generally are 9 to 11 amino acids with a V at P2 (position 2) and a K at the c-terminal position.

(Office Action, page 4.)

As noted above, the Examiner has stated that Guo teaches that CTL recognize viral peptides complexed with MHC and that peptides which bind HLA-Aw68 generally are 9 to 11 amino acids with a V at P2 and a K at the C-terminal position. (*See* Office Action, page 4.)

As emphasized by Dr. Sette in his Declaration, the Examiner has arbitrarily focused on only one of the potential HLA-Aw68 peptide motifs disclosed in the Guo publication. (Sette Declaration, ¶ 23.) Guo discloses more than this one motif. Guo also teaches that HLA-Aw68 peptides are characterized by a V at P2 and an R at the C-terminus; and a T at P2 and an R at the C-terminus. (*See id.*; Guo, page 364, Table 1.)

As further discussed by Dr. Sette, considering all of the motifs in Guo, and considering the entire ~3000 amino acid sequence of Chien, one of ordinary skill in the art would generate nearly 60 possible peptides looking at these references in combination. (*See* Sette Declaration, ¶ 24.) From these nearly 60 possible peptides, one of ordinary skill in the art would have no further guidance from Chien, Berzofsky, or

Guo to narrow down the possibilities to a fewer number of peptides, and certainly would have no information to select the claimed peptide.

The Examiner states that "*[i]t is also noted that there are only a small number of peptides encompassed by the motif taught by Guo et al.*" (Office Action, page 4.) As attested to by Dr. Sette, this statement made by the Examiner is misleading because Guo is only a subset of the number of possible options available to one of ordinary skill in the art in view of the prior art as a whole. (*See* Sette Declaration, ¶ 26.) Indeed, in Dr. Sette's opinion, looking only at Guo for guidance with respect to identifying a particular CTL-inducing peptide is not an appropriate analysis. (*See id.*, ¶ 27.)

Numerous additional motifs were disclosed and taught in the prior art at the time of filing of the present invention. These additional available motifs are highly relevant to the current analysis because, as stated by Dr. Sette, a researcher in the field at the time of filing of the present invention would have been as interested in identifying an immunogenic peptide having, for example, an A2 motif, as he or she would have had in identifying an immunogenic peptide having an A3 motif. (*See id.*, ¶ 28.) Similarly, a researcher in the field would also have been interested in identifying an immunogenic peptide having one of any number of motifs, each of which would have been an equally reasonable alternative. In fact, according to Dr. Sette, the HLA-Aw68 motif disclosed in Guo occurs relatively infrequently in the population as compared to several other motifs, such as A3 and A11, which are far more prevalent. (*See* Sette Declaration, ¶ 30.)

The Examiner states that "a routineer would have identified such peptides as potentially pertinent to the antiHCV response in HLA-Aw68 positive patients." (Office Action, page 5.) As Dr. Sette points out, however, the Examiner, disregards the point

that a "routineer," or a person of ordinary skill in the art, would have been equally interested in identifying peptides pertinent to an anti-HCV response in patients positive for numerous other individual HLA alleles. (*See* Sette Declaration, ¶ 28.) Dr. Sette further notes that a researcher in the field would likely be interested in identifying a peptide for inclusion in an HCV vaccine that would have broad population coverage. (*Id.*, ¶¶ 29-30.)

Examples of additional motifs known at the time of filing of the present invention include those of Jardetzky *et al.*, *Nature 353*: 326-327 (September 1991) ("Jardetzky") (Exhibit B). Jardetzky discloses an HLA-B27 motif where the peptides that bind to HLA-B27 are usually nonamers containing an R at P2, a positively charged amino acid at P1/P9, a hydrophobic amino acid at P3 and a nonpolar or small polar amino acid residue at P6. (*See* page 327, second column through page 328, first column.)

In addition, Hunt *et al.*, *Science 255*:1261-1263 (March 1992) (Exhibit C) discloses an HLA-A2.1 motif where peptides that bind to HLA-A2.1 are generally nine amino acids in length and have an L or I at P2 and an amino acid residue with an aliphatic side chain at P9. (*See* page 1262 column 3 through page 1263, column 1.)

As an additional example, Falk *et al.*, *Immunogenetics 38*: 161-162 (February 1993) (Exhibit D) describes peptide motifs of HLA-B35 and -B37, where the HLA-B35 motif is preferentially P, A, V at P2, K, D, E at P4, Y, E, M, L, I at P9 and the B37 motif is preferentially D, E at P2, V, I at P5, F, M, L at P8 and I, L at P9. (*See* Table 1, page 162.)

In Dr. Sette's view, a researcher attempting to identify an epitope of HCV that is recognized by T cells would have considered all known motifs, such as those as

disclosed in, for example, Jardetzky, Hunt and Falk, and not just the several motifs disclosed in Guo. (*See* Sette Declaration, ¶ 34.)

Applying Guo to Chien alone would result in nearly 60 possible CTL peptide candidates. As stated by Dr. Sette, applying the additional motifs as disclosed, for example, in Jardetzky, Hunt and Falk, in view of the entire HCV genome sequence, would result in hundreds or even thousands of CTL peptide candidates. (*See* Sette Declaration, ¶ 35.) This clearly is not a "small or easily traversed, number of options that would convince an ordinarily skilled artisan of obviousness." *Ortho-McNeil Pharm., Inc. v. Mylan Labs, Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008). Thus, in view of the cited art, one of ordinary skill in the art would not predictably arrive at Applicants' claimed peptide.

Furthermore, as pointed out by Dr. Sette, the identification of potential candidate epitopes based on motif is only a first step. In comparison to the cited art, the present application considers several factors other than the nature of the crucial anchor residues to identify specific HCV peptide epitopes. Examples of subsequent steps include: (1) determination of binding affinity of a potential peptide epitope; (2) cross-reactivity of potential peptide epitopes to two or more allele-specific HLA molecules; (3) conservancy among various diverse HCV isolates; and (4) determination of immunogenicity, such as demonstration of sequence-specific recall responses with subsequent challenge. (*See* Sette Declaration, ¶ 37.) Each of these subsequent steps serve to select the most promising epitopes useful for inclusion into a vaccine. (See Specification, Example 10, pages 79-81.)

Thus, as further emphasized by Dr. Sette, the sequence and/or motif of a peptide does not allow one to be able to predict whether a specific peptide would have desired characteristics according to the factors listed above. (*See* Sette Declaration, ¶ 38.) Thus, even given a finite number of identifiable peptides, one of ordinary skill in the art may still not arrive at a CTL-inducing peptide with the desired characteristics due to the high degree of variability in immunogenicity and binding that occurs even amongst a group of peptides having the same motif. Certainly, in the present situation, where the prior art does not provide a finite number of identifiable peptides, the factors described above would only result in additional variability and unpredictability.

Finally, Applicants have shown, as discussed by Dr. Sette, that the elected peptide GVAGALVAFK exhibits the strongest CTL-inducing response in transgenic mice as compared to any of the other peptides listed in Table XXIII and compared to any of the other peptides which share the same A3 motif. (*See* Sette Declaration, ¶ 40.) Applicants also point out that in Table XVI, Applicants' elected peptide GVAGALVAFK exhibits one of the strongest binding affinities as compared to over 400 other peptides which share the same A3 motif. (*Id.*)

Thus, as noted by Dr. Sette, the CTL-inducing and binding characteristics of the GVAGALVAFK peptide, as determined by Applicants, demonstrate that the GVAGALVAFK peptide has unexpected properties. (*See* Sette Declaration, ¶ 41.) In view of the improved binding properties of the GVAGALVAFK peptide as compared to over 400 other peptides sharing the same motif, and in view of the significantly greater CTL induction generated as compared to other peptides sharing the same motif, Applicants assert that evidence of nonobviousness and/or unexpected advantageous

properties is present. It is the functional characteristic of the peptide, as determined by the Applicants, which renders the peptide to have an unexpected property, and thus renders the peptide non-obvious in view of the prior art.

In *Takeda*, the Federal Circuit distinguished the facts of the case from those in another of their recently-decided cases, *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir. 2007). The Federal Circuit stated that in *Pfizer*, in contrast to *Takeda*, the "prior art provided 'ample motivation to narrow the genus of 53 pharmaceutically-acceptable anions disclosed by Berge to a few, including benzene sulphonate.' Here, the court found nothing in the prior art to narrow the possibilities of the lead compound to compound b." *Id.*

In the present case, none of the references cited by the Examiner provide the guidance as presented in *Pfizer* that would allow one of ordinary skill in the art to further narrow down the large number of possible HCV CTL epitopes that could be obtained. Further, Applicants assert that it would have been unpredictable, in view of the cited art, to arrive at Applicants' claimed peptide. Thus, in view of *KSR* and the subsequent decisions of *Takeda* and *Pfizer*, the present invention is not rendered obvious by Chien in view of Berzofsky or Guo.

The Examiner states that "it is routine in the art to test large numbers of peptides to idnetify immunogenic peptides from a desired molecule." (Office Action, page 4.) However, as the Federal Circuit has noted with respect to obviousness, "to have a reasonable expectation of success, one must be motivated to do more than merely to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave no indication of which parameters were critical

or no direction as to which of many possible choices is likely to be successful." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (internal quotations omitted).

Indeed, the Federal Circuit has also recently stated that the "Court in *KSR* did not create a presumption that all experimentation in fields where there is already a background of useful knowledge is 'obvious to try,' without considering the nature of the science or technology." *Abbott Labs*, 544 F.3d at 1352.

In the present case, where the number of possible candidate peptides is not a finite or predictable quantity, where significant experimentation would be required to narrow down this large number of possibilities, and where there is no guidance in the art as to what would be a particularly preferred peptide, it cannot be argued that the claimed invention is obvious based on such an "obvious to try" analysis.

Finally, the Examiner has reiterated that "the functional attributes of claim 166 would presumably be present in *the peptide of Chien et al.* in that said larger peptide would be processed in vivo to yield the peptide of claim 166." (Office Action, page 7 (emphasis added)) and has further stated that "there is no evidence of record that suggests that "*the peptide taught by Chien et al.* contains another immunodominant epitope that would suppress the response to the peptide recited in the claims" (*Id.* (emphasis added)). In each of these statements, Applicants assume that the Examiner is referring to the AA1850-AA1900 fragment of Chien when he discusses "the peptide taught by Chien et al." Applicants point out that the arguments with respect to functional attributes and peptide processing are made on an assumption that the AA1850-AA1900 fragment of Chien would be a starting point. However, as discussed in detail above,

there is absolutely no reason provided by the Examiner, or offered in the prior art, that would lead one of ordinary skill in the art to start with this particular peptide. The initial assumption is misplaced, and thus the argument is irrelevant until the Examiner can provide such a reason. The Examiner must "guard against slipping into use of hindsight and to resist the temptation to read into the prior art the teachings of the invention in issue." *Abbott Labs*, 544 F.3d at 1348 (*quoting Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966).

In view of the discussion above, Chien, in view of Berzofsky, and further in view of Guo does not render the claimed invention obvious. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be reconsidered and withdrawn.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

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Date: September 24, 2009

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